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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,956	10/10/2001	Xuehai Ye	64688/152	6226

7590 11/04/2002

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 11/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/972,956	Applicant(s) YE ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Action is in response to the amendment filed on 8/9/02 as Paper No. 8. The amendment filed 8/9/02 has been entered and claim 1 has been entered and claims 8-12 have been added.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Specifically, the declaration was amended by the insertion of the word "provisional" before the word patent. However, the alteration was made without initialing or dating the alteration.

Response to Arguments

2. Applicant's arguments filed 8/9/02 have been fully considered but they are not persuasive. Applicants argue that the substance of the Declaration has not been altered, and that the only alteration appears in the wording of the boiler plate form itself, wherein the word "provisional" was inserted in the form merely to identify the priority application whose serial number followed on the form.

3. In response, it is respectfully pointed out that all alterations of the declaration must be initialed and dated. Therefore, a new Declaration must be filed.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1-12 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and well established utility.

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The claims are drawn to a method for infecting the glomerular cells of the kidney of a mammalian subject with a recombinant adenovirus vector carrying a gene or genes of interest.

Credible Utility

Following the requirements of the Utility Guidelines, the first inquiry is whether a credible utility is cited in the specification for use of the claimed method. The only cited utility identified by the examiner is for the transfer of genes for treatment of various inherited and acquired renal disorders (see p. 2 of the specification). This is considered a credible utility.

Substantial Utility

The claims encompass the delivery of a reporter gene (lacZ) to glomerular cells (see claim 8). This is not a substantial utility because there is no "real world" use for delivering a reporter gene to glomerular cells. Utilities that are only useful for experimental purposes are not "real world" utilities. There is no disclosure in the specification or the prior art indicating a "real world" use of delivering a reporter gene to glomerular cells. Therefore, there is no substantial utility for the method.

Well Established Utility

Next, it is to be determined whether there are any well-established utilities for the method. The only asserted utility for the claimed method is for the delivery of genes to treat inherited and/or acquired renal disorders (i.e. gene therapy) (see p. 2 of the specification). Delivery of a gene of interest for therapeutic purposes is considered to be a credible utility. However, as mentioned above, the method does not have a substantial utility. Without a substantial "real world" use, the method cannot have a well-established utility. Therefore the method does not have a substantial or well-established utility, as required by 35 U.S.C. 101.

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a specific, substantial and well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As mentioned above, the only asserted utility that disclosed in the specification and that is recognized in the art is delivery of a gene of interest in order to treat a disorder (i.e. gene therapy). The asserted utility is not enabled for the reasons that follow.

The claims are drawn to a method for infecting the glomerular cells of a kidney of a mammalian subject with a recombinant adenovirus vector carrying a gene or genes of interest, including growth factor genes (see claims 9 and 10), chemikines (claims 11 and 12), and the reporter gene lacZ (claim 8). The specification discloses, "The rapid development of gene transfer technology provides an opportunity to develop treatments for various inherited or acquired renal disorders." (See p. 1, paragraph 2 of the specification). The delivery of an adenoviral vector carrying a gene of interest to glomerular cells in order to treat a disorder is a method of gene therapy. Therefore, the only asserted utility for the method is gene therapy, a credible utility for which the disclosure does not meet the enablement requirements of 35 U.S.C. 112, first paragraph.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

As mentioned above, the claims encompass using an adenovirus to deliver of a gene or genes of interest to glomerular cells in order to treat renal disorders. Therefore, the claims encompass gene therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims delivering an adenoviral vector encoding a gene of interest to the kidney glomerular cells of a mammalian subject. The subject can be any species of mammal, including rats and humans. Furthermore, the claims encompass treating any disorder associated with glomerular cells of the kidney in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to a target

disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples (see page 409, first col.). Crystal also teaches, "Among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity, and to enable the transferred gene to be regulated" (see p. 409, second column). Verma et al. (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section). Crystal also teaches that "humans are not simply large mice" and that predictions from gene transfer studies in animals has not been borne out in human safety and efficacy trials (see p. 409, first column).

Working Examples and Guidance in the Specification

The specification has no working examples, whatsoever, demonstrating delivery of a gene or genes of interest to glomerular cells to treat any renal disorder. The specification does provide examples demonstrating that the method can be used to deliver an adenoviral vector comprising a gene of interest to the glomerular cells of a rat kidney *in vivo*, and demonstrates that a non-therapeutic gene of interest (lacZ) can be delivered to and expressed in glomerular cells. Therefore, the examples address only one aspect of the unpredictability recognized in the art, namely the problem of delivery of the vector. However, it is pointed out that the examples

do not indicate that the vector is delivered specifically (i.e. only) to glomerular cells. For instance, the specification indicates that endothelial cells of the blood vessels also stained positive and that diffuse staining pattern of lacZ made it difficult to determine the exact cells types that were positive for lacZ expression (see page 12 of the specification). Also, the examples presented do not overcome any of the other art-recognized obstacles associated with gene therapy mentioned above. For instance, there are no examples or guidance that the vector can effectively express a therapeutic gene of interest, i.e. that the therapeutic gene could be properly expressed for the required duration of time and at an appropriate level to be effective. The examples only demonstrate delivery to glomerular cells *in vivo* in rats, and *in vitro* in human cells.

Also the specification does not offer any guidance on which diseases/disorders would be responsive to treatment, or even which genes of interest would be effective at treating renal disease/disorders or any guidance on the dosage and frequency of administration that is required to confer a therapeutic effect.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of the adenoviral system would first require that a gene of interest could be effectively delivered to glomerular cells such that the delivery resulted in the treatment of a renal disorder in vitro. The adenoviral vector comprising the therapeutic gene would then have to be tested in animal models of the disease in order to determine efficacy of the treatment in animals. Following successful treatment of animal models, the method would have to be tested by clinical trials in humans in order to determine efficacy and toxicity in human subjects. This would

require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy recognized in the art, the breadth of the claims, the lack of successful working examples demonstrating delivery of an effective amount of a gene to treat a disorder, the lack of guidance in the specification and the high degree of skill required, it is concluded that the amount of experimentation required to predictably deliver an adenoviral vector comprising a gene of interest to glomerular cells to treat a renal disorder is undue.

Response to Arguments

8. Applicant's arguments filed 8/9/02 have been fully considered but they are not persuasive.

Regarding the breadth of the claims, Applicants argue that claim 1 has been amended to remove the phrase "requiring same" and that the claim is drawn to a method for gene transfer to glomerular cells, thus the invention is not drawn to a method for treating any disease of the kidney. The amendment is noted and it is acknowledged that the claim does not read on treating any kidney disease, but as mentioned above, the claim is still very broad as it still encompasses the treatment of any disease associated with glomerular cells. Applicants contend that gene transfer of glomerular cells has been described in two species of mammals, and contend that this is sufficient to support the claims. Applicants cite a CCPA case (In re Gardner) in support of

their contention. In response, it is respectfully pointed out that the cited CCPA case was in reference to a rejection under 35 U.S.C. 112, second paragraph, as being indefinite. The instant rejection is under 35 U.S.C. 112, first paragraph. Therefore, the argument does not actually address the instant rejection under 35 U.S.C. 112, first paragraph, and are not persuasive. Furthermore, the specification only describes in vivo delivery of a reporter gene (lacZ) to glomerular cells only in rats, and in vitro delivery to human glomerular cells. The specification does not disclose the delivery of a gene of interest to glomerular cells such that the delivery results in the treatment of a renal disorder.

Regarding the unpredictability of the art, Applicants argue that demonstrating delivery a gene specifically to glomerular cells is all that is needed to support the claims, as the claims are drawn to a method of gene transfer, not gene therapy. It is respectfully pointed out, as mentioned above, the claims encompass the treatment of a renal disorder (i.e. gene therapy), and that the only asserted and recognized "real world" utility for the method is for gene therapy. Furthermore, there are no examples demonstrating that the method results in the effective treatment of a renal disorder. The specification only demonstrates the delivery of a reporter gene (lacZ) to rat glomerular cells in vivo (and human glomerular cells in vitro). As mentioned above, delivery is only one problematic issue of gene therapy. Other issues not addressed include the proper level and duration of gene expression required to treat renal disorders. There is no indication in the specification that a therapeutic gene can be expressed at the appropriate level and for the appropriate amount of time required to treat a renal disorder. Applicants argue that clinical trials in humans are required by the FDA, not the USPTO. It is acknowledged that human trials are not required by the USPTO. However, sufficient evidence has not been

presented demonstrating that the method overcomes the art-recognized problems associated with gene therapy, the only asserted and recognized utility for the method. However, given the unpredictability of gene therapy recognized in the art and the lack of working examples demonstrating successful treatment of a renal disorder using the method, there is no indication that the method would effectively treat e renal disorder in any mammal, including humans. Applicants point out that a reference dated 1995 was cited in the rejection (Crystal). It is respectfully pointed out that Crystal is only one of the references cited in the rejection; others include Verma (1997) and Walther (2000). Crystal teaches many of the problems associated with gene therapy that were recognized in 1995. Verma (1997) and Walther (2000) indicate that problematic issues recognized by Crystal in 1995 have still not been overcome. Applicants also assert that a number of patents have been issued which include gene therapy in the titles and contents and which do not indicate successful human trials. It is pointed that each application is examined on its own merits, and that the issue is not that no human trials have been conducted, but that there is no disclosure provided in the specification overcoming the unpredictable nature of gene therapy. An art that was recognized as unpredictable as early as 1995, and which still is not considered predictable. In order to overcome the unpredictability of gene therapy recognized in the art, the specification would have to disclose the effective administration of a therapeutic gene of interest to an appropriate animal model for human disease, a disclosure not present in the instant application.

Regarding the lack of working examples in the specification, Applicants contend that the working examples demonstrate delivery of a gene of interest to glomerular cells in vitro and in vivo. In response, it is acknowledged that the working examples indicate the delivery of a

reporter gene to glomerular cells in vitro and in vivo. However, the claims encompass the gene therapy, as mentioned above. The art recognizes several problems mentioned above regarding gene therapy, and the specification does not disclose any working examples which overcome the unpredictability of gene therapy methods.

Regarding the quantity of experimentation required, Applicants contend that clinical trials are not required and that the method of claim 1 satisfies all of the requirements for patentability. It is acknowledged that clinical trials are not required. However, there are no working examples demonstrating that the invention overcomes the problems recognized in the art, as mentioned above. Therefore, the method does not satisfy the 112 requirements.

9. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 is drawn to an adenoviral viral vector comprising a control element that preferentially expresses a gene of interest in renal glomerular cells. Therefore, the claim encompasses promoter elements for which no written description is provided in the specification. The specification discloses the use of the CMV enhancer and the chicken beta-actin promoter to express a gene of interest in glomerular cells. However, the CMV enhancer and chicken beta-actin promoter are elements which are known to confer constitutive gene expression in any cell type, and are not known to confer preferential expression in any particular cell type. Therefore, the genus of control elements that preferentially express a gene of interest in glomeruli is

represented in the specification by only the constitutive CMV enhancer and chicken beta-actin promoter. Thus, applicant has not adequately described a representative number of glomerular-specific expression elements.

The written description guidelines note "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, the function of the promoter elements is disclosed (preferential expression in renal glomerular cells), but no structural limitations or requirements (e.g. sequences which confer glomerular-specific gene expression) are provided for guidance on the identification of enhancer/promoter elements which meet these functional limitations.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, no structural features of the enhancer/promoter elements which confer the preferential expression of a gene in glomerular cells has been disclosed. Therefore, one of ordinary skill in the art would not know which elements confer glomeruli specific gene expression. It is respectfully pointed out that at the time of invention, there was not a single renal glomerular cell specific promoter known in the art, as evidenced by Wong et al. (Am. J. Physiol. Renal Physiol., Vol. 279:F1027-F1032, December 2000--after the filing date of the

instant application). Wong identifies a glomerular-specific promoter from the human nephrin gene (see first sentence of abstract) states, "this represents the first glomerular-specific promoter to be identified." (See abstract).

In Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of promoter/enhancer elements which preferentially express genes in renal glomerular cells, as the first glomerular-specific promoter identified was the glomerular-specific promoter from the human nephrin gene, in 2000 (see Wong). Therefore, the claims fail to meet the written description requirement by encompassing promoter elements which are not described in the specification.

Response to Arguments

10. Applicant's arguments filed 8/9/02 have been fully considered but they are not persuasive. Applicants argue,

> "Paragraph [014] of the specification provides in great detail the specific enhancer and gene promoter used in the reduction to practice of the invention. Paragraph [014] of the specification describes suitable control elements... It will be abundantly clear to the artisan to whom this patent application is addressed how to use the suitable control elements. These are well known in the art and, as such, need not be referenced"

In response, it is respectfully pointed that a "representative number" of glomerular-specific promoter elements have not been described in the instant application. No structural features (e.g. sequence) of elements which confer glomerular-specific gene expression have been described. As mentioned above, the first glomerular-specific promoter element was identified in

the year 2000, which was after the filing date of the instant application. Therefore, one of ordinary skill in the art would not have been able to identify elements which would confer glomerular-specific gene expression, based on the disclosure of the specification. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112, second paragraph

Response to Arguments

11. The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn.

Claim Rejections - 35 USC § 102

Response to Arguments

12. The rejection of claims under 35 U.S.C. 102(b) as being anticipated by Sukhatme (U.S. Patent 5,869,230) is withdrawn.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
October 31, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER